

MAYS. (Thos. J.)

DRUG INTERFERENCE.

READ BEFORE THE PHILADELPHIA COLLEGE
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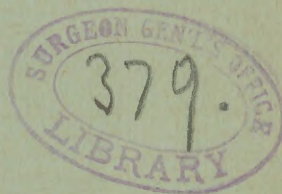
BY

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DRUG INTERFERENCE.

THE belief that "there is a remedy for every wrong" is as natural in a medical as it is in a moral sense. The savage, through an accumulated experience, has learned that by taking counteracting poisons he protects himself against the bites and stings of venomous animals ; sub-lethal doses of rattlesnake venom, as has recently been shown by Dr. Sewall, have a prophylactic influence against fatal doses of the same poison ; and Dr. Cash has likewise demonstrated that the administration of corrosive sublimate in divided and highly-diluted doses will secure immunity from otherwise fatal quantities of anthrax poison. On the other hand, it is also well established that between muscarine and atropine, between muscarine and pilocarpine, and between physostigmine and atropine, there exists a genuine antagonistic action.

In the February number of the THERAPEUTIC GAZETTE for the year 1885, and in No. 6 of the *Centralblatt für die Medizinischen Wissenschaften* for the same year, I published some experimental observations on drug an-



tagonism, in which I showed that, so far as the frog's heart was concerned, a marked antagonism existed between many of our most important remedial agents ; and the remarks in this paper will be chiefly based on the work there recorded. The apparatus which I employed was virtually the same as that described before the college in my essay on the "Nutritive Value of some Beef Extracts" (see *Transactions of College of Physicians*, 1886, vol. viii. p. 264 ; also *THERAPEUTIC GAZETTE*, March, 1886).

In judging this work, it must be borne in mind (1) that the frog's heart will continue to beat so long as it is supplied with nutritive material like blood, which was used in these experiments, or until it is overpowered or paralyzed by some poisonous agent ; (2) that the highest amplitude of the heart's pulsations while thus fed is a measure of its capacity for work ; hence the pulse-tracings obtained under such conditions are taken as a standard, with which all other tracings are compared ; and (3) that it is not intended that the heart should here serve as a circulatory organ, but merely as an organic medium, with which the action of therapeutic agents can be demonstrated. Now, it developed that on the addition of a small quantity of any drug to the blood the heart's contractions became fuller than those which were derived from blood alone ; while, on the contrary, larger quantities diminished the same in proportion to the amount which was administered. This is well shown in the following tracing, which was obtained from alcohol :

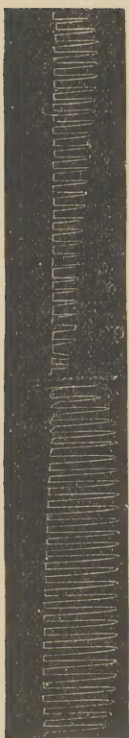
2 p. c. Blood sol.

Alcohol 1 : 2000.



1 : 666.

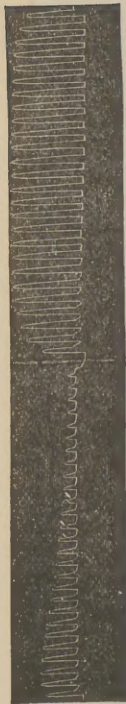
1 : 1000.





1 : 400.

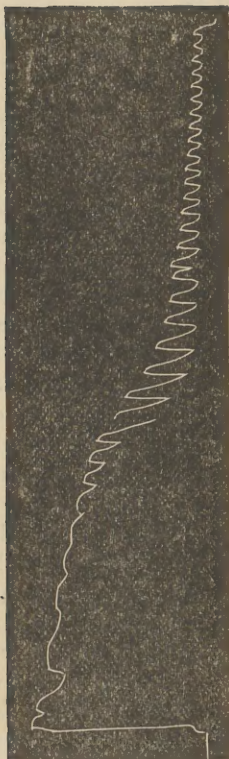
1 : 1000.



1 : 25.

1 : 1000.

1:5.



The first part of the tracing is given by a two per cent. blood solution alone, the second by 2000 parts of the same blood to 1 of alcohol, the third by 666 parts of blood to 1 of alcohol, and so on, until finally it was found that 1 part of alcohol to 5 parts of blood completely paralyzed the heart and arrested it in diastole.

It further appeared that those agents which showed an affinity for the heart's muscular irritability arrested it in diastole, and those which affected its nervous irritability arrested it in systole. Among the former are alcohol, ether, nitrous and chloric ether, chloroform, acetic and carbolic acids, aconitine, aloin, atropine, brucine, cannabin tannate, cocaine, curare, gelsemine, kairin, lycopine, quinine, resorcin, strychnine, veratrine, and all the potassium salts. Among the latter are caffeine, chloral hydrate, delphinine, digitaline, morphine, salicine, saponine, theine, and all the sodium and ammonium salts.

Every agent here named behaved in a way precisely similar to that of alcohol. Each one possessed a dose which gave higher heart-beats than could be obtained from blood alone, as well as a dose which entirely inhibited the heart's action. The former was called the minimum and the latter the maximum dose.

Now, when the minimum and maximum doses of some of these agents are once worked out, it appears that the minimum doses are direct antagonists to maximum doses. This is especially true of those agents which have an affinity for the heart's muscular irritability, and which arrest the heart in diastole. For example, a maximum dose of

chloroform of 1 part to 500 of blood solution will almost entirely inhibit the heart's action, but when a minimum dose of atropine or of curare be added to this dose and administered the cardiac pulsations will probably be nearly as high as they would be under the influence of minimum doses of either of these agents or of the two per cent. blood solution. This is well shown in the following tracings obtained from atropine and chloroform :

Atropine.
1 : 160,000.

Chloroform.
1 : 500.

Their combined effect.



The first part of the tracing was given by atropine and blood solution in the proportion of 1 : 160,000 ; the second part by chloroform and blood solution in the proportion of 1 : 500 ; and the third part by their combined effect.

The following tabular arrangement shows the pulse elevations in millimetres of the drugs which were found to possess these antagonistic properties :

	Names of drugs and their dilutions.	Pulse elevations in millimetres.
I.	Atropine 1 : 160,000	13
	Alcohol..... 1 : 25	4
	Their combined action.....	8
II.	Aconitine..... 1 : 160,000	15
	Ether 1 : 5	5
	Their combined action.....	10
III.	Curare..... 1 : 80,000	18
	Ether 1 : 10	10
	Their combined action.....	18
IV.	Atropine 1 : 160,000	10
	Ether 1 : 10	7
	Their combined action.....	10
V.	Atropine..... 1 : 160,000	8
	Chloroform..... 1 : 500	2
	Their combined action.....	9
VI.	Curare..... 1 : 80,000	12
	Chloroform 1 : 500	3
	Their combined action.....	9
VII.	Aconitine..... 1 : 160,000	16
	Chloroform..... 1 : 500	4
	Their combined action.....	15
VIII.	Ether 1 : 400	7
	Chloroform 1 : 500	3
	Their combined action.....	7
IX.	Strychnine..... 1 : 160,000	14
	Chloroform 1 : 500	9
	Their combined action.....	15

	Names of drugs and their dilutions.	Pulse elevations in millimetres.
X.	Veratrine.....I : 160,000	14
	ChloroformI : 800	13
	Their combined action.....	16
XI.	AconitineI : 160,000	16
	CurareI : 26	5
	Their combined action.....	15
XII.	AtropineI : 160,000	14
	CurareI : 50	10
	Their combined action.....	14
XIII.	AtropineI : 160,000	15
	StrychnineI : 1000	4
	Their combined action.....	14
XIV.	StrychnineI : 160,000	17
	Atropine.....I : 1000	4
	Their combined action.....	15

It is very evident that in all these instances there are at work two forces which are antagonistic in their action on organic tissue, the one tending to enhance its function and the other to interfere with it. These effects are displayed here as decidedly by drug interference as if they had been wrought by the two mechanical forces of attraction and repulsion, and they give us an exact mathematical demonstration that drugs have the power of supporting and preserving life when attacked by adverse forces. And if we recognize the fact that disease is but the manifestation of forces which move in a direction inimical to health, and if we substitute these for the operation of the maximum drug doses in the above illustrations, do we not have a clear picture before us as to how drugs combat dis-

ease,—viz., by interference? The fact of force interference is well established in the physical world. Two antagonistic sound-waves produce silence, two opposite undulations of light produce darkness, and who will say that a similar relation may not exist between drug and disease force? Who will say that a similar adjustment cannot be formed between most of our diseases and many of our varied and powerful therapeutic agents?

Associated with this power of interference, most, if not all, of our drugs possess the property of selecting and acting on special tissues without disturbing the surrounding structures. Hence we are justified in drawing the inference that given the knowledge of a drug, and of the tissues for which it has a special affinity, we can so regulate the dose of the former that it will enhance the vitality of, and may in this manner eradicate disease existing in, the latter.

The matter of dosage is a point which requires attention. It is probably more important to select the proper dose than the proper agent, if our aim is to secure the greatest possible amount of stimulation without engendering any toxic properties, for it was invariably shown in these experiments that minimum and not maximum doses had the power only of exalting vital action. This is demonstrated in all, and especially in the examples where atropine in minimum doses was the antagonist to maximum doses of strychnine, and conversely minimum doses of strychnine became the antagonist to maximum doses of atropine.

This power of special action is clearly de-

fined in the following well-known examples of clinical therapeutics. On account of a special affinity for the peripheral nerve-endings, atropine, in small doses, checks sweating and ptyalism, regulates the action of the heart, dilates the iris, and, by increasing intestinal peristalsis, it relieves constipation. Cantharides, owing to its affinity for the urinary tract, stimulates excretion of the kidneys, alleviates urethral irritation, and gives tone to the muscles of the bladder. Castor oil and aloes, on account of their elective action on the alimentary canal, the former on the upper and the latter on the lower part, are favorably known as agents for checking infantile diarrhœa when given in small doses. Pilocarpine, by acting on the sweat-centres, stimulates the cutaneous, salivary, bronchial, and lacteal secretions, and thus becomes a valuable remedy in many of the diseases which affect those structures.

Now, when these examples of definite therapeutic action are considered in connection with the experimental data which form the basis of this paper, I think they give us ground for hoping that those diseases, which are believed to be due to the action of poisons known as ptomaines and leucomaines, will find their fitting antagonists in the still undiscovered properties of our therapeutic agents. These toxic agents are analogous to our vegetable alkaloids both in chemical composition and in their behavior towards animal tissues. Professor Brieger extracted neurine, ethelendiamine, and muscarine from decomposing fish flesh, the latter of which is also obtained from the mushroom, *Agaricus mus-*

carius. In mammals, muscarine slows the pulse, lowers the blood-pressure, inhibits salivary and lachrymal secretion, increases pancreatic, hepatic, mucous, and cutaneous secretion, contracts the pupil, and produces powerful tetanic contractions of the stomach and intestines, as well as vomiting and diarrhœa. These muscarine phenomena, which are completely antagonized by atropine, as has been shown by Professor Schmiedeberg, give us in the main a typical outline of the familiar symptoms of gastro-intestinal catarrh in children, which are usually regarded as coming on without specific cause other than that of faulty diet and digestion. Professor Brieger also isolated several other animal alkaloids, one of which gives rise to severe intestinal peristalsis and diarrhœa, and the other, which he calls mydaleïn, is still more remarkable because it produces a marked rise in the bodily temperature. In guinea-pigs it increases the salivary, nasal, and lachrymal secretions, dilates the pupil, and the rectal temperature is increased from 1° to 2° C. At the same time there is marked increase in the peristaltic action of the intestines, great dyspnœa, paralysis, and gradual death. Typhotoxine, another ptomaine produced by the Koch-Eberth typhoid bacillus, causes salivation, paralysis, and exhaustive diarrhœa in animals (Wolff); tyrotoxicon, isolated from decaying cheese by Professor Vaughn, and believed by him to be the specific cause of cholera infantum; peptotoxine, formed during the digestion of fibrin by artificial gastric juice, and sepsine, a crystalline substance yielded by decomposing yeast, both very poisonous; the

atropine-like poison found in putrefying meat solution, and which probably produces the well-known symptoms of sausage-poisoning; the powerful poisons which have been extracted from the fæces and urine, and which may be responsible for many of the so-called digestive disorders, as well as for the little-understood disease known as uræmia; and the tetanus ferment, which has recently been shown by Dr. Shakespeare to possess the power of inducing tetanus in animals, all demonstrate the possibility that many of our most common diseases may depend on causes which are specific and alkaloidal in character, and which will some day be shown to have their true therapeutic antagonists.

With a view of widening the field of therapeutic knowledge, it may be asked what clew the considerations offered in this paper give us in reference to the discovery of new drug properties and their practical application to the process of disease? In answer, it may be stated that the first step which they indicate to be taken in this direction consists in ascertaining the tissue, structure, or cell for which any given drug or disease shows an elective action, and then to find the proper quantity of the drug which will prove antagonistic to the disease. The solution of this problem is, however, not so simple as it appears from the premises. For if we regard disease as the resultant of forces moving in a direction contrary to health, then we must also accept the alternative propositions that the forces which inaugurate disease consist of many varieties and shades, and that, in order to deflect these, a similar diversity of therapeutic resources are

required. Hence he who studies every case in detail from an independent stand-point, and who gives due consideration to every influence which we know is capable of moulding the processes of life, is a better practitioner than he who to-day mechanically prescribes that which benefited a similar case yesterday.

Let our experience be to us a general guide in the application of remedies, but let us also recognize the fact that the nature of the food, its metabolism and that of the tissues, occupation, climate, inheritance, diathesis, temperament, education, the moral, social, and religious state, the action and interaction of all the bodily organs, constitute a powerful set of forces, which vary in each and every individual, and which must not be left out of calculation if we wish to avoid the disappointments and pitfalls which are incidental to slipshod prescribing.

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